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RELATIVE EFFICACY OF HYDROCORTISONE AND METHYLPREDNISOLONE IN ACUTE SEVERE ASTHMA

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SYNOPSIS

Glucocorticosteroids play a key role in suppressing the inflammatory process in acute severe asthma. The choice and dose of a particular steroid has largely been determined empirically, whilst the the relative clinical efficacy of different types of intravenous steroids in acute severe asthma is not clear in published studies.

Hydrocortisone and Methylprednisolone are the most commonly used agents in this setting. A wide disparity in the costs of these two drugs necessitated the evaluation of their relative efficacy.

A randomised prospective study of Asthma Unit admissions over a three month period was conducted. The study design was guided by epidemiological principles with the purpose of answering the question posed at a pragmatic level.

Therapy consisted of 4-hourly nebulised salbutamol, intravenous aminophylline and either Hydrocortisone 200mg 4-hourly IVI or Methylprednisolone 125mg 12-hourly IVI. Patients whose treatment differed from the basic protocol as well as those who required further intensification of therapy were analysed separately. The endpoints of the study were 1) the time taken to achieve maximum peak expiratory flow rate in hours and 2) the duration of hospital admission.

386 patients were admitted to the Asthma Unit. After exclusions 191 patients were used in the analysis (Hydrocortisone n=91, Methylprednisolone n=100). The groups were comparable with respect to baseline data. The median time to maximum Peak Expiratory Flow Rate was 19 hours for Hydrocortisone and 23 hours for Methylprednisolone (median

test, p=0,21). Median duration of Asthma Unit stay was 30 hours for Hydrocortisone and 36 hours for Methylprednisolone (median test, p=0.01). A similar significant difference was shown when comparing patients who had been on prior oral maintenance steroids. In those patients with an admission duration greater than 48 hours, the methylprednisolone group had achieved a lower percentage of predicted peak expiratory flow rate (56.9%) compared to the hydrocortisone group (71.8%). This difference was statistically significant (p=0.009 Mann-Whitney U test).

It was concluded that, at the dosages selected, Hydrocortisone is more effective than Methylprednisolone in acute severe asthma. Methylprednisolone has an advantage in that its use produces considerable saving in terms of nursing time and consumable expenditure (needles,swabs, syringes). At the time of the study methylprednisolone was considerably cheaper than hydrocortisone. It was therefore felt that practical considerations (cost and convenience) should be accorded greater influence in the clinical choice of steroid particularly as the difference in efficacy which was shown was not striking.

CONTENTS

LIST OF ILLUSTRATIONS

GLOSSARY OF ABBREVIATIONS

HC	Hydrocortisone
MP	Methylprednisolone
PEFR	Peak Expiratory Flow Rate
FEV_1	Forced expiratory Volume in 1 second

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND:

The pathophysiological changes in acute severe asthma include bronchoconstriction, mucous plugging and an inflammatory response in the airways. The fact that inflammation is a critical feature in the pathogenesis has been increasingly appreciated since the post mortem demonstration of widespread airway inflammation following death from asthma.[1] The suppression of this process with glucocorticosteroids has become standard practice since the MRC trial in 1956[2] and many subsequent studies.[3,4,5]

Glucocorticosteroids exert their anti-inflammatory action by modulation of several cellular and biochemical pathways[6] which are not completely understood. In the setting of acute severe asthma, hydrocortisone (HC) and methylprednisolone (MP) are the most commonly used glucocorticosteroids. The administration of these glucocorticosteroids in equivalent biopotent doses produces equivalent anti-inflammatory activity and it is often assumed that their relative clinical efficacy is similarly equal. The comparison of these corticosteroids has not formed part of any previously published large clinical study.

1.2 OBJECTIVES OF THE STUDY:

This study aimed to examine the relative clinical efficacy of HC and MP in acute severe asthma. An important part of the study was to conduct the investigation as part of the normal functioning of the Asthma Unit and to compare the two steroids using the doses and dose-intervals in common clinical use at Groote Schuur Hospital. In view of

increasing financial constraints, the need to determine the most cost-effective therapy has become a priority in this institution.

1.3 OBJECTIVES OF THE DISSERTATION:

The dissertation aims to i) place this clinical research in perspective with regard to previous work in this field, ii) justify the research methods and iii) review the results and issues arising from them.

1.4 METHODS:

The study was an open prospective parallel randomised trial of HC 200mg 4-hourly IVI vs MP 125mg 12-hourly IVI in acute severe asthma. All Asthma Unit admissions over a 3 month period were eligible for the study. Data was collected on all asthmatic admissions to the hospital during the study period. (The methods employed in this study are described in detail in Chapter 6.)

1.5 LIMITATIONS AND CONSTRAINTS:

The study received no support in the form of grants, drugs or equipment from any external source.

1.6 CHAPTER OUTLINE:

The second chapter of this work defines the clinical research problem and outlines the background which prompted this research. Chapter 3 examines glucocorticosteroids and the theoretical basis for their efficacy in asthma as anti-inflammatory agents. Previous clinical studies of the efficacy of glucocorticoids in acute severe asthma are

reviewed in Chapter 4 with special reference to their statistical power and steroid dosage. The following chapter outlines i) the basic principles of research methodology as applicable to this study , ii) the relevance of the chosen study design and iii) problems in clinical studies of acute severe asthma. The methods of the study (described as an interventional survey) are described in Chapter 6. The results of the study and their statistical analysis are presented in Chapter 7. A discussion of the results follows in Chapter 8, where the issues of drug costs and cost-efficacy are raised. Finally, conclusions based on the results are drawn and recommendations are made.

CHAPTER 2: THE CLINICAL RESEARCH PROBLEM

The use of glucocorticosteroids in acute severe asthma is accepted clinical practice. However the choice of corticosteroid as well as the specific doses and dose intervals are still controversial.

The two glucocorticosteroids examined in this study are those in most common clinical use at Groote Schuur Hospital. There is disagreement amongst clinicians as to which drug is more effective. In addition there is a wide disparity in the cost of the two drugs. The need to rationalise escalating drug expenditure prompted this study to determine which agent was more effective as well as cost-effective.

The clinical research problem was therefore primarily to examine their relative clinical efficacy. Furthermore the study would have to demonstrate the difference (if any) based on a population sample which is representative of the majority of acute severe asthmatics seen at Groote Schuur Hospital.

As far as implementation of the study was concerned, a prime objective was that it be conducted in the course of the ordinary functioning of the Asthma Unit without the unrealistic influences which a strict protocol-driven experimental design would impose. In order to satisfy these objectives a large sample population was necessary. An observational or epidemiological method of study was therefore adopted. By adhering closely to the principles of experimental study design (with randomisation and a clearly defined management protocol), the use of the observational method might still be possible in this situation and thus could be termed an interventional survey.

The hypothesis on which the research was based was that (on the grounds of biologic equipotency at the chosen dosages) both corticosteroids were equally effective. However it was anticipated that, although similarly effective, practical considerations of cost and convenience might favour MP. At issue, therefore, was whether cost considerations may be pre-eminent; for, while MP requires much less nursing time to administer as a 12-hourly regimen (HC was given 4-hourly), this advantage would only be clinically relevant if overall hospital stay was similar for both agents (or favoured MP).

CHAPTER 3: GLUCOCORTICOSTEROIDS AND ACUTE SEVERE ASTHMA

3.1 STRUCTURE:

Glucocorticosteroids are composed of a cyclopentenophenathrene ring with varying side groups to form a 21 carbon molecule (Figure 1)[7]. Hydrocortisone has a double bond between C4 and C5, ketone groups at C3 and C20, and hydroxyl groups at C11, C17 and C21. In methylprednisolone there is a double bond between C1 and C2 (increasing anti-inflammatory and decreasing mineralocorticoid action) and an additional methyl group at C6.[8]

3.2 PHARMACOKINETICS AND PHARMACODYNAMICS:

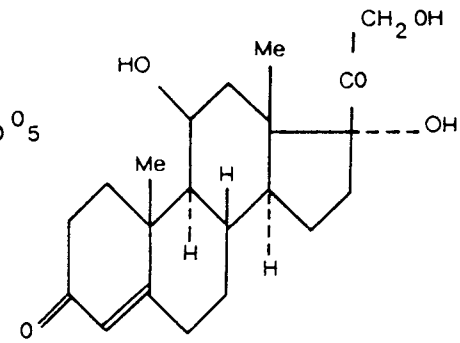
Following absorption and distribution, factors which affect the availibility of free steroid include the extent of binding to plasma proteins, the rate of degradation and the steroid's affinity for intracellular receptors. In the case of cortisol 75% is bound to transcortin and 15% to albumin.[9] When the cortisol concentration is increased it eventually saturates this protein binding and the quantity of free (active) steroid is greatly increased. Structural differences in steroid analogues interfere with protein binding and thus increase the fraction of steroid which is metabolically active.[8]

Variations in the structure of different glucocorticoids, as well as differences in absorption, distribution, steroid receptor binding and elimination influence the magnitude and duration of their effects.[10]

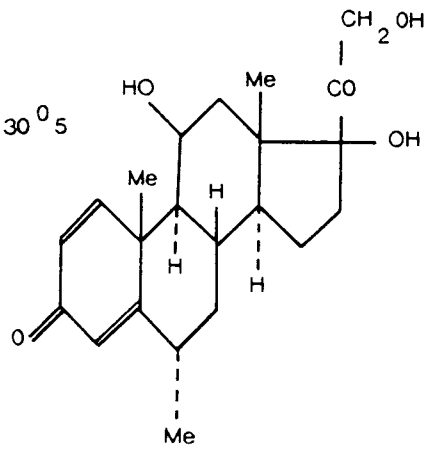
Cortisol is inactivated in the liver by reduction to acidic compounds and then conjugation with glucuronic acid. The latter step imparts water solubility and allows renal

Figure 1: Chemical Structure of HC and MP:
(from British Pharmacopoeia (7))

Hydrocortisone: $C_{21}H_{30}O_5$



Methylprednisolone: $C_{22}H_{30}O_5$



elimination. The metabolism (or rate of excretion) of corticosteroids is increased by hyperthyroidism, diphenylhydantoin, adrenaline, primidone, oestrogens and rifampicin.[8] In contrast to this, metabolism or excretion is decreased by hypothyroidism, hepatic cirrhosis, renal disease and, in the case of MP, erythromycin and troleandromycin.[8] The relative plasma half-lives and potency of HC and MP are illustrated in Table I (from Dunlap and Fulmer[8]).

TABLE 3.1: RELATIVE POTENCY AND HALF-LIVES OF HYDROCORTISONE AND METHYLPREDNISOLONE.

	Hydrocortisone	Methylprednisolone
Anti-inflammatory potency	1	5
Equivalent dose (mg)	20	4
Mineralocorticoid potency	++	+
Biologic $t_{\frac{1}{2}}$(hours)	8-12	12-36

Schwartz et al found that plasma clearance of HC was increased in patients requiring greater than 15mg of prednisone a day in order to maintain asthmatic control.[11] These patients also had a diminished eosinopaenic response to cortisol at 4 and 6 hours after the the study dose. Dwyer et al reported increased clearance of HC in some steroid treated asthmatics.[12] Absorptive differences, however, may be as important as those in elimination rate in determining peak plasma levels. Subsequent studies have shown no differences in the pharmacokinetics of prednisolone in normal and asthmatic subjects including patients who have received prolonged corticosteroid therapy.[13,14] Schenfield[15] found that three weeks of prednisone therapy in asthmatics had no effect on the plasma half-life of HC although there was considerable variation in peak plasma levels within and between patients. Because of the

interpatient variability in plasma levels of cortisol achieved following intravenous HC, high doses were advised in order to consistently achieve the plasma levels recomended by Dwyer. Schenfield's findings are in agreement with those of Wilson et al[14], who found considerable inter-patient variation in bioavailibility after a standard dose of prednisolone.

The conflicting findings of earlier studies and the large corticosteroid doses reported to be required by some asthmatics may be partly explained by differences in the patients studied, prior steroid dosages, duration of steroid therapy and differing steroid receptor sensitivity. Furthermore the possible simultaneous use of other drugs (particularly barbiturates) may have had significant effects on steroid metabolism. An additional important confounder in all studies of acute asthma is the duration of the attack (which influences the degree of inflammation and mucous plugging).

Response to glucocorticosteriods has been studied in animal models to evaluate the effect of different dosing strategies. In an animal model developed by Boudinot et al[10], a tenfold increase in the dose of prednisolone did not produce a proportional increase in effect (with hepatic tyrosine aminotransferase used as a marker). The maximum response increased by 50% and the duration of response was only doubled. In a subsequent study it was observed that smaller doses administered more frequently are much more effective than large single doses.[16] Reiss et al[17] examined a single (40mg) dose methylprednisolone regimen and compared this to a split dose regimen by measuring the effect on blood histamine and plasma cortisol. Their results indicate that the duration of effect can be more successfully extended by use of a smaller total dose in a divided manner.

3.3 INFLAMMATION IN ASTHMA:

Airway inflammation is now regarded as an integral part of asthma. Post mortem studies[18,1] of patients who died during status asthmaticus have described the inflammatory changes of oedema and an inflammatory cell infiltrate in the airway wall (eosinophils, neutrophils, plasma cells and lymphocytes). Furthermore there is epithelial damage and sloughing, basement membrane thickening and hyperplasia of goblet and smooth muscle cells.

The inflammatory cells release mediators that cause airway hyperresponsiveness. After allergen exposure in a sensitive patient there is a release of mediators primarily of mast cell origin resulting in immediate bronchoconstriction and increased airway secretions (early phase response). Additional mediator release and sustained bronchoconstriction with the recruitment of eosinophils and neutrophils follows several hours after significant allergen exposure (late phase response). These events result in damage to the epithelial lining and exposure of receptors to irritant stimuli. A detailed discussion of the inflammatory-cell biology in the pathophysiology of asthma is beyond the scope of this dissertation. The role of mediators such as histamine, eicosanoids and cytokines and the associated cellular events in this process are reviewed by McFadden and Gilbert.[19] Despite the incomplete understanding of the cellular and biochemical mechanisms highlighted in this review, there is ample evidence of an inflammatory process in the airways of patients with asthma.

As a result of this new understanding, the primary goal of therapy is increasingly directed towards resolving inflammation. Glucocorticosteroids are the most potent agents available for this purpose.

3.4 MECHANISM OF GLUCOCORTICOSTEROID ACTION:

Mechanisms of action which have been proposed for glucocorticosteroids in asthma include their effect on leukocyte traffic and function, altered chemotaxis, impaired mediator synthesis and release, enhanced beta-adrenergic receptor activity and decreased vascular permeability.[20,21]

According to the general model of steroid hormone action, steroid hormones bind to cytoplasmic receptors.[6] The receptor-hormone complex is then translocated to the nucleus where the synthesis of specific mRNA is induced. The effects of the steroid are only seen after the subsequent protein synthesis. The nature of the response in the affected cell is determined by its state of differentiation and further modulated by its metabolic and hormonal state.[22] A further point is that the duration of action of the steroid will vary according to the half-life of the induced protein.

CHAPTER 4: CLINICAL STUDIES OF GLUCOCORTICOSTEROIDS IN ACUTE SEVERE ASTHMA.

4.1 INTRODUCTION:

In 1956 the MRC trial[2] showed that oral cortisone acetate produced superior improvement compared to placebo in patients with status asthmaticus who had been unresponsive to 24 hours of conventional therapy. Subsequent studies have demonstrated that glucocorticsteroids hasten the improvement in lung function and facilitate recovery from hypoxaemia.

Although corticosteroids are used in the management of acute severe asthma, their optimal dose and duration of therapy are not clear from published studies.

4.2 EVIDENCE OF CORTICOSTEROID EFFICACY:

4.2.1 TYPE II ERROR IN PREVIOUS STUDIES:

Numerous studies are frequently cited in support of a particular corticosteroid and its dosage although many of the studies lack the statistical power necessary for such a claim to be valid. The importance of the type 2 error in clinical trials in acute severe asthma has been examined by Ward.[23] In the trials which were examined[3,4,5,24] comparing corticosteroids with placebo, all had a probability of less than 60% of detecting 25% more bronchodilation in those treated with corticosteroids. The study by Fanta[5] was the only one of these which showed a statistically significant difference between corticosteroids and placebo. Although this study did not have a greater power, the large difference in response resulted in its significance.

Fanta's careful study[5] of refractory asthmatics showed that corticosteroids speed the recovery from airflow obstruction. Twenty patients with acute severe asthma of comparable severity refractory to a combination of sympathomimetics, methylxanthines and B_2-stimulants were randomised in a double blind fashion to receive placebo or HC (2mg/kg bolus and then 0.5mg/kg/hr). During the 24 hour follow up period, there was no response at six hours but a significant difference favouring the steroid was evident at 12 hours and continued until the end of the study. The method used in the study excluded those likely to respond to bronchodilator therapy without the use of corticosteroids and the results demonstrate the efficacy of a dose of HC in the region of 1000mg/24 hours.

Pierson et al[3] found that PaO_2 improved in children with acute asthma treated with corticosteroids but there was no effect on asthma symptoms or pulmonary functions. There was a significant potential for bias in this study as a result of repeated breaking of blinding and reassignment of patients from the control to the study group.

McFadden et al[4] showed no advantage in using up to 1000mg of HC when compared to placebo. However when the period of observation was extended beyond 6 hours a difference was noted.[5]

4.2.2 OTHER EVIDENCE OF EFFICACY:

Other good evidence for the efficacy of corticosteroids in acute severe asthma comes from the two following randomised placebo-controlled trials: the study by Fiel et al[25] showed that MP administered in the emergency unit decreased the need for repeat emergency unit care. These findings are supported by those of Littenburg and Gluck[26] who showed a 60% decrease in the admission rate of patients with acute severe asthma (FEV_1 <50% of predicted) presenting to the

emergency unit and treated inter alia with a single intravenous dose of MP (125mg).

4.2.3 NEGATIVE STUDIES:

Kattan et al[27] and Luksza[28] were unable to find any reduction in the degree or severity of asthma in corticosteroid treated patients when compared to controls. Luksza compared the PEFR in 60 patients with acute severe asthma treated with or without low-dose corticosteroids (HC 400mg daily) with 30 patients treated with high dose steroids (HC 1200mg daily). They found no significant difference in the rapidity of relief of airflow obstruction using the higher dose compared to low dose or no steroids. The study interpretation is complicated by the possible presence of coexistent diseases and the lack of randomisation. A disturbingly high proportion of the cases required mechanical ventilation (13/90). The findings of this study have never been repeated in a comparable group of asthmatics.

Morell et al[29] studied 82 patients with acute severe asthma. This randomised double-blind trial divided the patients into three groups who received intravenous MP every 4 hours at doses of 10mg/kg or 2mg/kg or placebo. There were no significant differences in the baseline status of the three groups nor in their rates of recovery. One cannot conclude however, on the basis of their results, that corticosteroids are ineffective. The wide scatter in PEFR values may have obscured the results and the authors make no statement regarding the power of the study. In those patients who had failed to respond by the third hour of treatment, and in those who were previously taking oral corticosteroids, a favourable effect was seen in the high dose steroid group. Although this was not statistically significant, this does not necessarily exclude a clinically important difference.

4.3 CORTICOSTEROID DOSE:

4.3.1 GENERAL:

The wide variation in recommended doses of glucocorticosteroids results from the relatively few controlled studies of dosage. In addition many of these studies are impossible to interpret because of poor definition of patient populations, presence of pulmonary infections or inadequate indices of response.

4.3.2 DWYER HYPOTHESIS:

Dwyer[12] first suggested the need to achieve levels of plasma cortisol >100ug/100ml to alleviate severe attacks of asthma. This group found that, following the intravenous administration of 100mg HC, the steroid dependent asthmatics had lower plasma cortisol levels compared to those never on steroids. Their suggestion that high plasma levels are necessary was, in part, based on the need to increase the unbound (active) plasma cortisol fraction and thus increase the biologic activity of administered corticosteroids. The validity of conclusions drawn in this study remain in doubt in view of the small study population (7 cases) and the absence of objective criteria for severity of asthma or response to therapy. In addition no information was provided to indicate the interval between steroid administration and clinical response.

In order to achieve the levels recommended by Dwyer and avoid a progressive rise in serum cortisol levels a dose of 3mg/kg HC every six hours has been recommended.[30]

Collins et al[30] used a dose of HC between about 1000mg and 1750mg per 24 hours and achieved plasma levels in excess of 100ug/dl. Plasma cortisol levels were no different between those asthmatics who had and those who had not received previous corticosteroid therapy.

Fanta et al[5] found no significant correlation between plasma cortisol levels and improvement in lung function.

Thus although the Dwyer hypothesis is theoretically attractive, its validity has not been confirmed.

4.3.3 DOSE COMPARISON STUDIES:

Previous comparisons of "low" vs. "high" dose corticosteroids for acute asthma have failed to show any advantage in the use of high doses.[4,28,31,32]

A study by Britton et al[33] compared low, medium and high dose corticosteroids (the equivalent of HC 280mg, 840mg and 3500mg per 24 hours respectively). Their use of three different steroids via two different routes makes detailed comparison difficult. Furthermore their medium dose group was initially worse with a significantly lower mean PaO_2. Nevertheless their study could show no advantage over the medium dose in the use of a very high dose of HC (equivalent to >3g/24 hours).

A double blind study of intravenous MP by Tanaka et al[32] (comparing the equivalent of 400mg HC with 2500mg HC per 24 hours over a seven day period) showed no significant difference in the pattern or magnitude of spirometric response. This study is, however, also impaired by the use of a small sample of 10 patients where the two groups were poorly matched (with the low dose group having a 25% higher baseline FEV_1).

In an attempt to determine the optimum dose of corticosteroids, Haskell et al[24] studied a small group of adults with acute severe asthma (FEV_1 <30% of predicted). Patients were blindly randomised to receive intravenous MP every 6 hours for 3 days at doses of 15, 40 or 125mg (low, medium and high dose) and response in FEV_1 was measured. The low dose group failed to improve during the 3 days of

the study. The high dose group improved significantly by the end of the first day and the medium dose group improved by the middle of the second day. This suggests that a MP dose of 15mg 6-hourly is inadequate although the minimum dose for a response and the ceiling of the dose-respnse curve are unknown. No other studies have suggested that a dose-response relationship exists.

The effectiveness of low doses of corticosteroids has recently been reported by Bowler et al.[34] In a double blind comparison of HC 50mg, 100mg and 500mg intravenously every 6 hours for 48 hours they could find no difference in efficacy between the doses. Once again this study dealt with small numbers (n=66) and a type II error could not be excluded. In addition the duration of the attack of acute severe asthma was longer in the low dose group. These patients may therefore have been in the recovery phase of their illness, thereby obscuring any difference in treatment effect. Six hours after admission these patients had PEFRs of 60-70% of predicted and there was a more than twofold increase in FEV_1 in the first 24 hours. This suggests the existence of the confounding effect of rapidly reversing airflow limitation in some subjects.

4.4 PREVIOUS COMPARISON OF HYDROCORTISONE AND METHYLPREDNISOLONE:

In the only previous study of the relative efficacy of HC and MP in acute severe asthma, Sue et al[35] concluded that there were no clinical or statistically significant differences in the short term airway responses of patients treated with equivalent doses of corticosteroids. A group of 14 adult males was given either HC 100mg, MP 20mg or dexamethasone 3.75mg intravenously 6-hourly for 72 hours. At 12 as well as at 18 hours the MP group showed an unexplained transient deterioration. The difference in mean percentage of predicted FEV_1 favouring HC over MP was

significant at 18 hours ($p<0.05$) but not at other times (12 and 24 hours). In the light of previously cited studies showing the efficacy of higher doses of steroid, the doses used may have been too low to demonstrate a glucocorticosteroid effect.

The authors concluded that the steroids were equally effective while acknowledging that there was a large margin for type 2 error in relation to the sample size. They felt that a clinically significant difference was unlikely to become apparent in a larger study. However the question was raised of possible cost saving (assuming equivalent efficacy) by less frequent dosing of longer-acting corticosteroids such as MP.

4.5 META-ANALYSIS OF PREVIOUS STUDIES:

A recent meta-analysis[36] of 30 randomised controlled trials in acute severe asthma confirmed that the early use of corticosteroids in the emergency room reduces admissions to hospital in both adults and children. The data also indicated that oral steroid treatment in patients discharged from an emergency department significantly reduced the relapse rate at 7 to 10 days following treatment. With a baseline relapse risk of 20%, six patients would need to be treated to prevent one relapse. If the baseline admission risk is 20%, eleven adults would need to be treated to prevent one admission. It is only in the situation of a very low baseline risk of each complication (<=5%) that not using steroids could be justified.

In the analysis of data on high dose (equivalent to >1200mg HC/24 hours) vs moderate (620-1200mg/24 hours) or low dose (200-600mg/24 hours), there was a tendency to an advantage over placebo in only the moderate and high dose groups. Although the optimal dose could not be determined, it was

suggested that doses of less than 600mg HC/24 hours are suboptimal.

In the examination of the time course of improvement in pulmonary function in the studies comparing intravenous steroid and placebo, there was a significant difference between individual study results (heterogeneity) at 12 and 24 hours. A moderate "effect size" (0.34) was present in the paediatric group at 24 hours. The "effect size" on pulmonary function at 36 hours was small (0.2) without significant heterogeneity. The heterogeneity, when present, could not be explained on the basis of differences in the study populations or study design. The authors proposed that because of both a lack of sensitivity and within patient variability of pulmonary function tests, small but important changes were not detected. In the light of this, the need for studies to be large (as pointed out by Ward [23]) remains important and is not satisfied by most of the published work in this field.

4.6 SUMMARY:

Corticosteroids are clinically useful especially in patients not responding to bronchodilators. Their use in acute severe asthma is now standard practice. Glucocorticosteroids have been shown to decrease morbidity, hospitalisation and the need for repeat emergency room care. The choice of specific steroid has, however, been largely determined empirically. The optimum steroid dosage remains undetermined. There appears to be no advantage in using very high-dose (equivalent to HC >3g/24 hours) over lower dose corticosteroid (equivalent to HC ±1.2g/24 hours). However low doses in the region of 300mg HC/24 hours have not consistently been shown to be effective. The use of the equivalent of 1200mg HC/24 hours in this study may be regarded as appropriate in the light of these published

studies. In addition, a clinically important treatment effect is unlikely to be missed because of under-dosing.

MP has several theoretical advantages over HC which include: greater anti-inflammatory potency, longer duration of action and less sodium retaining properties than a bioequivalent dose of hydrocortisone.

CHAPTER 5: CLINICAL STUDY DESIGN IN ACUTE SEVERE ASTHMA

5.1 INTRODUCTION:

The following discussion serves as an outline of the principles which guided the design of this study in line with the study objectives (Chapter 1) and the clinical research problem (Chapter 2). Some of the particular problems in the study of acute severe asthma are addressed.

The design and interpretation of clinical studies in this situation presents several problems. Major aspects are the varying degrees of severity and rates of deterioration as well as causes of the acute attack; each of these is expected to influence the rate of recovery. The inherent variability of asthmatic airflow limitation leads to difficulties in assessing response to treatment.[37]

5.2 STUDY DESIGN:

5.2.1 EXPERIMENTAL AND OBSERVATIONAL STUDIES:

In the field of comparative impact research being considered here, the basic study design may be broadly divided into those with purely experimental and those with observational approaches.

In experimental studies the intervention is under the control of the researcher with the aim being to determine how outcome is affected by changes in the independent variable. In contrast to this the researcher does not control the intervention in observational studies, but rather observes the effects of an experiment "in nature". The key element which distinguishes experimental from observational studies is randomisation. A major advantage of the former type of study is that (with an adequate sample

size) groups are more likely to be comparable because most extraneous variables should be balanced.

However, since experimental studies often take place in an artificial setting and amongst a selected sample, the study population may differ from the target population with regard to important characteristics. If the effects of treatment depend on these characteristics, the observed effect in the study population could differ from the effect that exists in the target population. A potential advantage of observational studies is that they are often carried out in a setting in which the study population is more representative of the target population. Neither form of study is uniformly superior in every situation. The study should preferably be judged by how it meets specific objectives and constraints.

In experimental and observational studies the underlying philosophy is the same. That is to say a group of patients is taken in a baseline state, subjected to an intervention or manoeuvre and the impact in terms of outcome is recorded.

Although the underlying intellectual reasoning is the same, in epidemiologic research differences from traditional scientific research arise in the conduct of the research activity as a result of pragmatic, logistic and other constraints. These similarities and contrasts are described in detail by Feinstein[38] in his book on the architecture of clinical research.

5.2.2 SAMPLING, VALIDITY AND STUDY COST-EFFECTIVENESS:

The method of sampling study subjects is important if one would like to generalise the findings in the sample population to the target population. An accepted method would be by random sampling. The alternative epidemiological method would be to sample the entire target population (eg all Asthma Unit admissions), provided that

significant numbers of the target population were not missed by being treated elsewhere. Some degree of precision may be lost by such total target population sampling, but the validity of findings is probably of greater importance. In other words the study should provide an approximate answer to the correct question rather than a precise answer to the wrong question. Precision can then be enhanced by stratification (eg by degree of airflow obstruction/reversibility) at the analysis stage. Subsequent generalisation to the entire target (sampled) population may then be possible.

The randomised controlled trial remains the gold standard of clinical research but is not the sole acceptable method. The quality of observational studies can be improved by regarding the randomised controlled trial as a model to guide study design at an intellectual level rather than as a prescribed practical method of investigation. Gray-Donald and Kramer[39] suggested that in order to enhance validity one should follow as closely as possible the methods of good experimentation and test the scientific hypothesis in as many different ways as possible. By decreasing measurement error, avoiding sources of bias and using tools such as inclusion and exclusion criteria, one may obtain a result which approximates that obtained by a purely experimental study. Caution should, however be exercised if numbers are small and if the results are not striking.

Inevitably a trade-off occurs between the perfect study design and its practical implementation. A balance is sought between the total value of derived information relative to actual expenditure. In the final choice of study design an attempt is made to gather the most accurate information for a given cost (time, money or personnel).

5.2.3 CONFLICTS IN DESIGN AND ANALYSIS:

There are two basic policies (both of which are reasonable and justifiable) which are used in the design and analysis of clinical studies. Depending on the question being asked and the answers which are sought, one or other of these approaches may be preferred. The approaches that emerge often lead to conflict between supporters of each policy. [38]

The primary goal of a trial is usually obvious and demonstrates the outcome of an intervention in the groups under comparison. The secondary objectives, however, reflect the underlying purpose of the study and the standards to be used in interpreting results.

A difference in the philosophic approach to these two objectives gives rise to two divergent policies. Feinstein [38] calls these pragmatic and fastidious policies. In his pragmatic approach "a trial is intended to ask questions and obtain answers that are directly pertinent for decisions in clinical practice." In contrast to this, the fastidious approach requires that a trial be an explicitly scientific activity. A single study is seldom able to placate both viewpoints.

5.3 MONITORING OF RESPONSE:

The pulmonary function test used to monitor reversal of airflow limitation should be both sensitive and simple to perform. PEFR measurement has the advantage that it can be used in a wide spectrum of patients from all but the most severe to those in a stable state. A drawback of the PEFR is that it is effort-dependent. The pattern of response with serial PEFRs is clinically useful especially where a large decrease in airflow limitation with repeated testing is seen (as in acute severe asthma), and may outweigh this disadvantage. The final choice of test for monitoring is an exercise in compromise and it is doubtful whether additional

measures of pulmonary function would be of added benefit in the type of study described here.

5.4 DEFINITION OF OBSTRUCTION AND REVERSIBILITY:

There is no consensus in the literature on the definition of obstruction nor on what represents reversibility in bronchodilator studies. Eliasson and De Graff examined how criteria employed for obstruction and reversibility, used to define patient populations, result in a variation of results.[40] They found that the outcome of a bronchodilator trial is affected by the degree of airflow obstruction of patients enrolled. Because of the effect of regression towards the mean, the lower the initial pulmonary function, the greater is the likelihood that a subsequent measurement will show improvement (independently of any drug effect). As a result of this, as well as a minimal negative correlation of response with spirometry values, the most obstructed groups will show the greatest bronchodilator response. These effects are exaggerated when change in FEV_1 is calculated as a percentage of the initial value. The use of absolute values or the calculation of response as a percentage of predicted are probably more appropriate expressions of reversibility.

Eliasson and De Graff also point out the large overlap in bronchodilator response between diseases defined by the terms "reversible" and "irreversible" airflow obstruction.[40] A group of patients labelled as having asthma defined in terms of bronchodilator response, is likely to be heterogenous and may include patients with chronic obstructive lung disease.

CHAPTER 6: PATIENTS AND METHODS

6.1 STUDY DESIGN:

This study was designed as an interventional survey in order to answer the research question at a pragmatic level. That is to say, an intervention was performed (randomisation between HC and MP) in a semi-experimental fashion; outcome was then reviewed using an observational method. The study was "epidemiological" in the sense that no attempt was made prospectively to match individual cases in one study limb with those in the other. This ensured the recruitment of the maximum number of patients over a three month period.

The primary objective here was to examine the relative clinical efficacy of HC and MP. The secondary objective was to examine the issue of relative cost-effectiveness.

6.2 STUDY POPULATION:

All patients admitted to the Asthma Unit of Groote Schuur Hospital were studied over a three month period commencing 1 November 1989. This Asthma Unit forms part of the Emergency Unit and during 1989 had a total of 2067 admissions.

6.3 ROUTINE THERAPY:

All patients who present to Groote Schuur Hospital's Emergency Unit with acute severe asthma and who fail to show a satisfactory clinical response to nebulised B_2-stimulants and intravenous aminophylline within two hours are routinely admitted to the Asthma Unit. All cases receive 4-hourly nebulised salbutamol and intravenous aminophylline. The dose of aminophylline is based on estimated lean body mass

and adjusted when serum theophylline levels become available as described in the unit operating protocol in Appendix I. Asthmatics whose conditions are complicated by other medical illnesses and those needing intensive care are admitted elsewhere in the hospital.

Except in the mildest cases, intravenous steroids were routinely administered; the trial required that either hydrocortisone (200mg 4-hourly IVI) or the equivalent dose of methylprednisolone (125mg 12-hourly IVI) be used. The criteria for the initiation of steroid therapy are indicated in Table 6.1. The first dose of steroid was almost always given within an hour of presentation to the emergency unit.

In those cases not responding to this therapy, a salbutamol infusion could be added. Decisions to intensify therapy (eg. by adding a salbutamol infusion), to discharge patients or to admit a patient to an Intensive care Unit or general medical ward were taken by Emergency Unit staff (guided by the Unit operating protocol) independently of research personnel.

TABLE 6.1

CRITERIA FOR THE INITIATION OF STEROID THERAPY

1. All patients who received corticosteroids in the preceding three months as part of their maintenance asthma treatment.
2. All patients admitted to the Asthma Unit during the preceding 4 weeks.
3. Failure to show a satisfactory response* within 1 hour to nebulised salbutamol and intravenous aminophylline.
4. All patients who on a previous admission to the Asthma Unit showed a slow recovery curve and/or required intravenous steroids.

* Satisfactory response defined as: An improvement with regard to general state of distress, reduction of tachycardia and pulsus paradoxus and improvement of PEFR by 50% or more.

6.4 RANDOMISATION:

The steroid available for use in the Asthma Unit was alternated on a weekly basis throughout the study period. Changeover took place at 07h00 every Monday. Patients continued to receive the steroid given on admisson for the duration of their hospital stay or until converted to oral prednisone.

6.5 MANAGEMENT PROTOCOL:

During the trial period the criteria for (i) admisson to the Asthma Unit, (ii) therapy with bronchodilators and/or steroids, (iii) referral to the Intensive Care Unit and (iv) discharge from hospital were not different to those in place

for the preceding seven years. The specific discharge criteria are described in Table 6.2.

TABLE 6.2:
DISCHARGE CRITERIA

ALL 3 CRITERIA TO BE FULFILLED

1. No features of distress and able to walk to the toilet.
2. PEFR showing an upward trend and/or plateaued at more than 70% of the patient's best PEFR in the past year (or, if not available, predicted normal PEFR) **AND** morning dipping is not below 50% of the patient's best PEFR in the past year (or predicted normal PEFR)
3. Patient feels that he/she would be able to cope at home.

6.6 MONITORING:

As a result of the issues raised in paragraph 5.3, patients were monitored, as usual, by charting 4-hourly PEFR measurements. Daily serum theophylline levels were performed. The same Wright's mini peak flow meter was used on all patients and was checked daily on a non-asthmatic control. Serum electrolytes, urea and creatinine, arterial blood gases, chest X-ray and sputum cultures were performed when indicated on clinical grounds.

6.7 ENDPOINTS:

Two primary endpoints were used, these being (i) the time taken to achieve maximum PEFR (in hours) and (ii) the duration of Asthma Unit stay.

6.8 DATA COLLECTION:

The hospital notes of all patients admitted to the Asthma Unit were reviewed upon their discharge. The time taken to achieve maximum PEFR in hours was calculated from the time of arrival in the emergency unit to the maximum PEFR recorded on the peak flow chart.

As the exact time of discharge is relatively arbitrary and difficult to determine, each day was divided into 6-hour time units (00h00-06h00, 06h00-12h00, 12h00-18h00, 18h00-24h00). The duration of stay was then calculated in time units from the time unit of arrival in the emergency unit to that of discharge. A note was made of the need for salbutamol infusion and the need for Intensive Care Unit or medical ward admission. The prior use, if any, of oral maintenance steroids was recorded.

6.9 INCLUSION CRITERIA:

Patients were required to show evidence of reversibility of airflow obstruction with an initial increase in PEFR >20% (over the value on presentation) after the first salbutamol nebulisation had been administered, or an overall increase in PEFR >100% at any time during the admission.

In addition, patients were required to meet strict criteria for the severity of asthma, namely that the initial PEFR was less than 50% of the predicted value. Predicted PEFR was calculated according to Cote's formula[41] as follows:

Females: [Height(metres) x 6.23 - 0.035 x Age - 1.88] x 60

Males: [Height(metres) x (6.58 - 0.025 x Age)] x 60

As indicated in paragraph 5.4, these criteria will have selected the more obstructed patients. However as the main endpoints did not include a direct comparison of

bronchodilator response, this is unlikely to have affected outcome. In addition, the group studied is likely to have included some patients with chronic obstructive lung disease with a "reversible element" to the airflow limitation.

6.10 EXCLUSION CRITERIA:

Patients with evidence of other cardiorespiratory disease (eg. pneumonia, pneumothorax, pulmonary oedema or severe chronic obstructive lung disease) were excluded from further analysis. Those patients whose therapy deviated from the basic protocol were analysed separately, as were those who were transferred to a medical ward or intensive care unit.

6.11 ACUTE SEVERE ASTHMATICS NOT INCLUDED IN THE STUDY:

In order to determine how representative the study group was of the overall hospital asthmatic population, the records of all patients with acute severe asthma admitted elsewhere in the hospital during the study period were examined. Cases were identified by scrutinising the emergency unit patient registers and identifying admissions in whom a diagnosis of asthma was recorded or a nebulised B_2-stimulant was administered.

6.12 ETHICAL APPROVAL AND CONSENT:

Patients were informed that a study was being conducted using two forms of corticosteroid treatment of similar effectiveness. Their verbal consent to participaton in the study was obtained. The study was approved by the University of Cape Town Medical School Ethics and Research Committee.

6.13 STATISTICS:

The Chi-square, Student's t, Mann-Whitney U and Median tests were used when appropriate to determine the significance of findings when comparing the HC and MP groups, as well as the four subgroups: Hydrocortisone and maintenance steroid, methylprednisolone and maintenance steroid, hydrocortisone without maintenance steroid and methylprednisolone without maintenance steroid.

CHAPTER 7: RESULTS

7.1 STUDY POPULATION AND EXCLUSIONS:

386 patients were admitted to the Asthma Unit during the study period. The following categories were excluded from further analysis: i) 38 patients who had previously been diagnosed as suffering from chronic obstructive lung disease, non-asthmatics and patients who received oral theophylline therapy; ii) 58 patients who did not meet the study criteria for reversibility of airflow obstruction and/or the criteria for acute severe asthma; iii) 47 patients who were not given intravenous corticosteroids of whom 18 were treated with oral corticosteroids; iv) 33 patients who required the addition of a salbutamol infusion to the standard therapy; v) 19 patients who were transferred to the medical wards.

Table 7.1 shows the comparative proportions of patients in the MP and HC groups that were treated with more intensive therapy in the form of intravenous salbutamol (in addition to the usual regimen) and also shows patients transferred to the medical wards. The indications for transfer to a general medical ward were: associated medical illnesses (4), asthma unit full (1), persistent bronchospasm or judged to be unstable (14). No patients were transferred to the intensive care unit.

7.2 BASELINE COMPARISONS:

Thus, after the exclusions detailed above, analysis was confined to 191 patients; 91 in the HC and 100 in the MP groups respectively. Analysis of baseline data showed the groups to be comparable. No significant differences were seen between the MP and HC groups in age, predicted PEFR or PEFR as "percentage of predicted" after the first nebuliser was administered. The relevant data is illustrated in Table 7.2. Significantly more males were present in the MP group. Almost equal numbers of patients were on oral maintenance steroids at the time of admission.

TABLE 7.1
PATIENTS EXCLUDED FROM ANALYSIS

	HC n=150	MP n=151	CHI-SQUARE
SALBUTAMOL INFUSION n=33	8.7%	13.3%	p=0.20
WARD ADMISSION n=19	7.3%	5.3%	p=0.47

TABLE 7.2

COMPARISON OF BASELINE DATA

	HYDROCORTISONE n=91	METHYLPREDNISOLONE n=100	P value
Mean Age-years (±SD)	41.1±16.6	42.6±17.1	0.53 t test
Mean predicted PEFR (l/min)	486 [368/456]	415 [376/533]	0.72 Median test
Median adnmission PEFR -% of predicted	24 [17.2/33.6]	24.9 [18.8/30.8]	0.89 Mann-Whitney U
Male Gender (%)	18.7	31	0.05 Chi-Square
Prior Maintenance Steroid (%)	48.4	48.5*	0.99 Chi-Square

* Data missing in one case

[] Denotes values of 25th and 75th centiles

7.3 ENDPOINT ANALYSIS:

7.3.1 TIME TO MAXIMUM PEFR:

The median time to maximum PEFR was 19 hours for HC compared to 23 hours for MP. This trend favouring HC did not reach statistical significance (p=0.21). In view of the non-Gaussian distribution of values (illustrated by the box plots in figure 2) the (non-parametric) Mann-Whitney test was used. The mean maximum PEFR (percentage of predicted) which was achieved did not differ in the two groups [HC 81.5% ($\pm$20.3) vs MP 81% ($\pm$21.6); p=0.87 t test].

7.3.2 DURATION OF HOSPITAL STAY:

The median asthma unit stay was 30 hours (5 six-hour time units) for HC compared to 36 hours for MP. This difference was statistically significant (p=0.01, Median test). The wide range in hospital stay as illustrated in figure 3 is accounted for by a few patients with prolonged admissions. The difference in hospital stay is illustrated more clearly by plotting duration of hospital stay as a "survival curve" as shown in figure 4. A difference is apparent within 12 hours and continues beyond 36 hours.

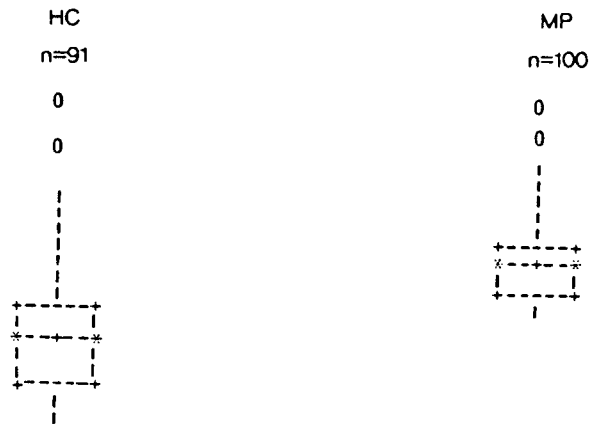
In order to compare the status of the small number of patients in the two steroid groups with a more prolonged hospital stay, the median PEFRs (% of predicted) were examined. After 24 hours, the HC and MP groups had achieved equivalent percentages of predicted PEFR. However, at 48 hours after admission, the HC group had achieved a median of 71.8% of predicted PEFR, which differed significantly from the 56.9% of the MP group (p=0.009, Mann-Whitney U test). These comparisons are shown in Table 7.3.

Figure 2: Time To Maximum PEFR (HOURS)

Maximum	66	109
75th centile	31	33.75
Median	19	23
25th centile	12	14
Minimum	3	2

Mann Whitney U test p=0.21

Figure 3: Duration Of Hospital Stay (HOURS)



Maximum	108	132
75th centile	42	48
Median	30	36
25th centile	18	18
minimum	6	6

Median Test p=0.01

Figure 4: Duration of Hospital Stay (Survival Curve)

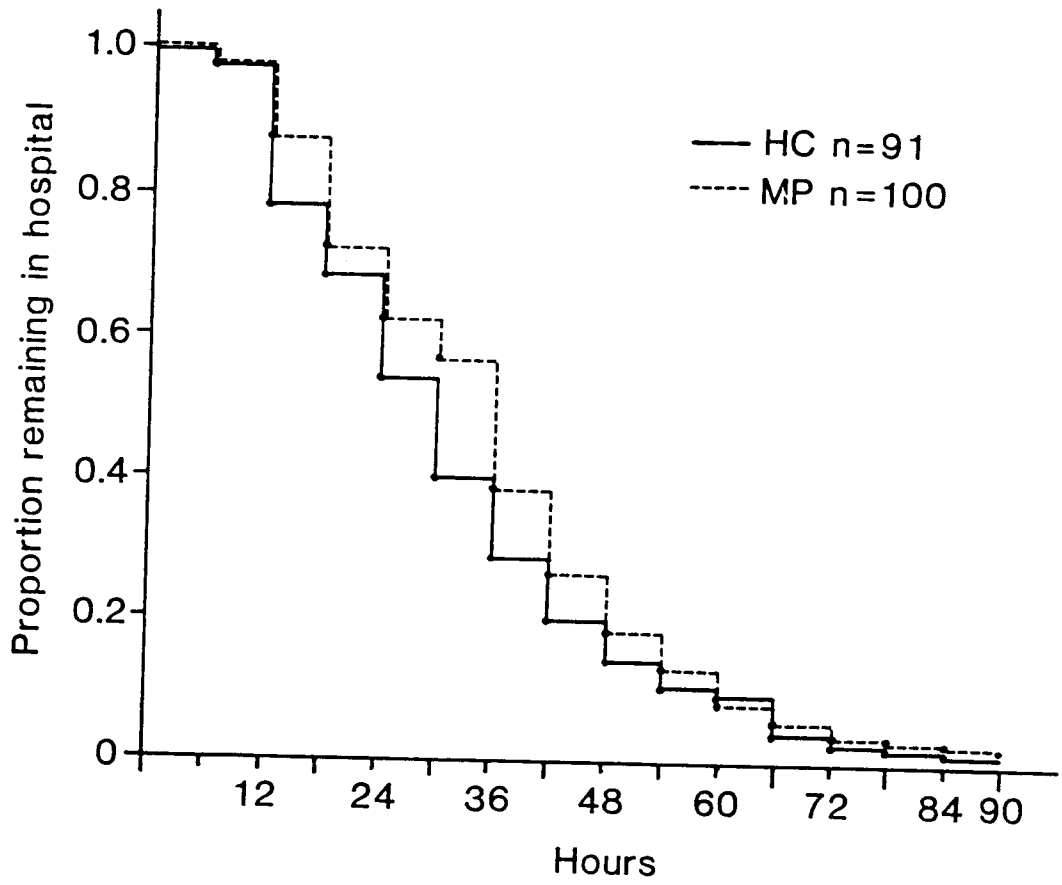


TABLE 7.3

PEFR ACHIEVED AFTER 24 AND 48 HOURS

	HC	MP	MANN-WHITNEY U
24 HOURS			
n=	58	72	
%predicted PEFR	70.7	68	P=0.99
	[54.7/85.0]	[56.6/86.9]	
48 HOURS			
n=	19	24	
%predicted PEFR	71.8	56.9	P=0.009
	[57.4/81.9]	[50.8/61.0]	

[] Denotes 25th and 75th centiles.

7.4 SUBGROUP ANALYSIS:

The HC and MP groups were subdivided according to prior oral maintenance steroid therapy. The comparison of the four resultant subgroups is shown in Table 7.4. The HC patients not on maintenance steroids were significantly younger than those who had been on maintenance steroids. Once again, a difference favouring HC is seen in the duration of hospital stay and this reached statistical significance in those who were on oral maintenance steroids before admission. No other significant differences were evident between these subgroups.

TABLE 7.4
SUBGROUP COMPARISONS-PRIOR MAINTENANCE STEROIDS

Maintenance Steroid*	HYDROCORTISONE Yes n=44	HYDROCORTISONE No n=47	METHYLPREDNISOLONE Yes n=48	METHYLPREDNISOLONE No n=51
Age (years)	45.5[¶] (35/56.8)	33[¶#] (23/45)	44[#] (29.3/56.8)	41 (27/49)
Predicted PEFR-l/min	400 (348/469)	418 (379/456)	423 (368/552)	406 (381/486)
Admission PEFR-% predicted	22.2 (16.9/30)	25.4 (18.3/35)	27.4 (18.8/35)	23.2 (17.7/28.6)
Maximum PEFR-% predicted	78.8 (61.5/97)	84.5 (71.3/95.1)	81.1 (67.0/96.7)	76.4 (67.6/90.6)
Hours to maximum PEFR	18 (10/28.5)	23 (12/33)	22.5 (16/30.5)	24 (12/35)
Hospital Stay-Hours	30[S] (18/30.5)	30 (18/42)	36[S] (24/48)	36 (18/42)

Median values quoted throughout with 25th and 75th percentiles in brackets below.

Mann-Whitney U test employed in all cases except Hospital Stay where Median test used.

* Data missing in one case, [¶] p=0.01, [#] p=0.02, [S] p=0.01

All other comparisons not significant.

7.5 THEOPHYLLINE LEVELS:

Theophylline level estimations were performed on serum samples drawn daily at 08h00. The results are reflected in Table 7.5. A large proportion of patients had subtherapeutic serum levels. This proportion did not vary appreciably over three days except in the HC group where a progressive rise in the percentages with toxic levels was seen.

TABLE 7.5
THEOPHYLLINE LEVEL ESTIMATIONS

DAY	1	2	3
HYDROCORTISONE			
Number tested	82	37	12
Subtherapeutic (%)	42.7	48.6	33.3
Therapeutic (%)	53.7	40.5	50
Toxic (%)	3.7	10.8	16.7
METHYLPREDNISOLONE			
Number tested	96	53	13
Subtherapeutic (%)	39.6	39.6	38.5
Therapeutic (%)	51	54.7	53.8
Toxic (%)	9.4	5.7	7.7

Theophylline level reference ranges:

Subtherapeutic: <55 umol/l
Therapeutic: 55-110 umol/l
Toxic: >110 umol/l

7.6 PATIENTS NOT INCLUDED IN STUDY:

29 patients with a possible diagnosis of acute severe asthma were admitted elsewhere in the hospital during the study period. Review of individual case records showed that 10 of these had previously been diagnosed as having severe fixed airflow obsruction. Therefore 19 asthmatics admitted elsewhere in the hospital were not included in the study data.

These cases were distributed as follows;

A. Medical ward admissions (n=12):
i) 10 cases with asthma asssociated with other medical illnesses (pneumonia 7, pulmonary tuberculosis 1, pneumothorax 1, severe bronchitis 1)
ii) 2 cases with acute severe asthma

B. Intensive care unit admissions (n=7):

Patients with acute severe asthma complicated by other medical illnesses are not considered suitable for Asthma Unit management. Six of the intensive care unit admissions required mechanical ventilation and intubation was performed shortly after arrival in the emergency unit. The two patients with acute severe asthma uncomplicated by other illnesses (who were admitted to the medical wards) were more severe asthmatics as they had both previously required mechanical ventilation and had carbon dioxide retention on admission arterial blood gas analysis.

CHAPTER 8: DISCUSSION

8.1 INTRODUCTION:

Difficulties inherent in the clinical study of the treatment of acute severe asthma have been discussed earlier. The effects of the heterogeneity of the asthmatic population with variable rates of recovery, severity of asthma, drugs used and their dosages cannot be overlooked. In view of the limitations in previously cited studies, a large number of cases was entered into this study in order to eliminate type 2 error in relation to sample size.

8.2 ENDPOINTS:

The HC group appeared to achieve maximum PEFR values sooner than the MP group. A similar difference favouring HC is seen in the "HC with maintenance steroid" subgroup. Neither of these differences, however, proved to be statistically significant.

From the literature reviewed earlier, it is clear that there is a delay in the onset of action of corticosteroids which amounts to several hours. In both groups there were patients who achieved maximum PEFRs shortly after admission. These early responders would probably improve on bronchodilators alone irrespective of steroid therapy. The use of non-parametric significance testing obviates the possibility of these patients concealing differences between the HC and MP groups.

A significantly longer duration of hospital stay was seen in the MP treated patients. This was true of the steroid groups as a whole (MP n=100 vs HC n=91) as well as in the

subgroup which had been on oral maintenance steroids prior to admission.

Figure 4 clearly illustrates the comparison of hospital stay in the HC and MP groups. In the initial few hours there is no difference. Thereafter the numbers in the HC group decrease more rapidly until, beyond 48 hours there are small numbers in each group with no difference between the two. Further analysis of these "long stayers" would be inappropriate as it is from amongst these patients that the group transferred to the medical ward was drawn. Of the 19 patients transferred to a medical ward, 52.6% were in the Asthma Unit for 48 hours or longer prior to transfer.

The study exclusion criteria would have had a significant effect on this subgroup, which is likely to have included severe asthmatics, patients with chronic obstructive lung disease and possibly so-called steroid resistant asthmatics.[37]

The validity of the difference in the duration of hospital stay is supported by the additional observation that, in those remaining in the Asthma Unit after 48 hours, the MP group had achieved a lower percentage of predicted PEFR. The consistency of the pattern favouring HC in both major endpoints of the study lends further support to the validity of the findings.

This consistent pattern remains when the entire sample population is examined, although with decreased significance levels on statistical analysis. Appendix 2 reflects the results obtained when examining the sample population as a whole, excluding only non-asthmatics and ward transfers (i.e. irrespective of the need for salbutamol infusion and the criteria for obstruction and reversibility).

8.3 ISSUES ARISING FROM THE CONDUCT OF THE STUDY:

The choice of study design (including randomisation) ensured that the study was performed by the Asthma Unit staff in the normal course of their duties with a minimum of departures from their usual treatment schedules. The survey was conducted in the emergency unit with a staff of 18 full-time and about 12 sessional doctors. Individual doctor bias with regard to admission or discharge is therefore unlikely to have systematically affected the study. The results obtained highlight the relative efficacy of hydrocortisone and methylprednisolone in a commonly encountered clinical situation.

During the study period only 3 cases of acute severe asthma not complicated by other illnesses or requiring mechanical ventilation were admitted elsewhere in the hospital. The sampled population can therefore be regarded as being representative of the uncomplicated hospital asthmatic population.

In view of the generally short duration of admission and inaccuracies in determining the exact moment of discharge, the use of 6-hour time units was useful and more appropriate than timing an admission in terms of days or hours. The difference in median duration of admission was only one time unit. This does not necessarily indicate a difference of 6 hours and may conceal a smaller or larger difference. An analagous situation is seen with the PEFR monitoring. For obvious reasons this cannot be measured continuously but is done at intervals (in this case 4-hourly). Time to maximum PEFR could equally therefore be viewed as comprising 4-hour time units.

8.4 ISSUES ARISING FROM THE STUDY RESULTS:

The HC and MP groups are well matched in terms of age, baseline status and previous maintenance steroid therapy. The difference in gender distribution is unlikely to have had any bearing on outcome. In particular, one should note the absence of any difference between the steroid groups with respect to the number of patients excluded from analysis because of ward transfers or need for a salbutamol infusion. The absence of any intensive care unit transfers indicates that, on the whole, the emergency unit staff correctly reserved the Asthma unit for patients who were not critically ill.

The cases studied here all met strict criteria for severe asthma and reversibility of airflow obstruction and were not complicated by other acute illnesses. Therapy in hospital was carefully standardised with nebulised B_2-stimulants and aminophylline infusions. There was no control of, nor was any attempt made at adjustment for other factors, such as precipitants of the acute severe asthma, duration of the acute attack at the time of admission or therapy received prior to arrival at the hospital. The absence of attempts to "control" for the above features in any given patients was, again, consistent with the practical demands of a busy Asthma Unit service; at the time of admitting patients in the acute phase of an attack, doctors are rarely able to predict the likely subsequent course with confidence.

A large proportion of patients had sub-therapeutic theophylline levels although this did not differ appreciably between the two steroid groups. It is unlikely that this factor resulted in any difference in outcome between the HC and MP groups. The theophylline levels shown in this study are a reflection of inadequate therapeutic drug monitoring in the Asthma Unit due to cost constraints. Instead, an elaborate method for calculating the dose for each patient is used (see Appendix 1). Monitoring over the past few

years has consistently shown that application of the formula results in 50% therapeutic levels, 10% toxic levels and the remainder subtherapeutic - a pragmatically acceptable mix (S J Louw, personal communication July 1993).

8.5 OTHER CONSIDERATIONS:

One might speculate why, despite the advantages of MP discussed earlier, this steroid performed less well than HC in the clinical situation. The optimal dosage interval is not known for the longer acting steroids and the 12-hourly dosing schedule may have been too wide. However the administration of MP at intervals approximately equal to half the biologic half-life would generally be regarded as appropriate. Secondly there is a possibility that the frequent peaks in plasma cortisol achieved with 4-hourly HC administration may have some added effect in certain asthmatics. This question is particularly relevant in the light of the experimental work by Boudinot and others referred to in paragraph 3.2. If their findings are valid, the 4-hourly dose scheduling of HC would have placed it at an advantage over MP. Finally it is possible, although unlikely, that the inadvertent omission of a dose of a drug might have a significant effect especially if doses are widely spaced.

In recent years the need for intravenous as opposed to oral steroids has been questioned. Jonsson et al[42] reported that the oral administration of steroids was as effective as intravenous use in their patients with moderate exacerbations of asthma (FEV_1 $\pm$40-50% of predicted with moderate hypoxaemia). There was no advantage to the addition of parenteral to high dose oral steroids in the study by Harrison et al[43] of patients with severe asthma (PEFR <30% predicted) without ventilatory failure. More recently, Ratto et al[44] compared oral and intravenous MP and again could show no difference in improvement in FEV_1,

duration of hospitalisation and rate of improvement in pulmonary function. These patients had mean admission FEV_1 (% predicted) of 26-27% (and were therefore of comparable severity to those reported here) but had a mean hospitalisation of more than three days. The degree of reversal of airflow obstruction after 24 hours of treatment was equivalent to that obtained in this study.

These studies by Jonsson, Harrison and Ratto were analysed in Rowe's meta-analysis[36] and the results showed that the effect on pulmonary function of oral and intravenous steroids were equivalent. The marked cost saving with oral steroids makes their use an attractive option.

8.6 RELATIVE COST-EFFECTIVENESS:

Although HC appears to be more effective in this study, this is not equivalent to superior cost-effectiveness. No previous studies have presented a practical model for drug-drug cost-effectiveness evaluations in acute asthma. The proposed model for drug cost-effectiveness analysis by Gagnon and Osterhaus[45] requires the determination of an effectiveness ratio for each drug. This was done by multiplying the "probability of healing" (with the use of each drug) by the "proportion not affected by a clinically important (adverse) condition." An effectiveness to cost ratio was then obtained by dividing each drug's effectiveness ratio by its cost. The data obtained in this study does not lend itself to this type of calculation.

The actual cost to the hospital for these corticosteroids at the time of the study was HC(1200mg) R32.52 and MP(250mg) R17.78.[46] The cost, in terms of corticosteroid alone, of treating a patient with HC for the median admission period of 30 hours would amount to R37.94. In the case of MP (median admission 36 hours) the cost comes to R26.37.

In addition to the cost advantage of using MP in terms of drug costs alone, other factors need to be considered. In evaluating cost-effectiveness, the daily cost of a theoretical "hospital bed," consumables (needles, swabs, syringes, etc) and duration of admission should be included. If MP is administered 12-hourly, it results in a 2/3 reduction in consumable expenditure and nursing time as compared to 4-hourly HC. For this reason MP is strongly favoured over HC by nursing staff in the Asthma Unit. Nevertheless the costs of intravenous corticosteroids do vary from time to time and the clinician needs to regularly review the relative cost advantages in the light of relative drug efficacy. As an example, the current (1993) costs of intravenous steroids at Groote Schuur Hospital are: HC (1200 mg) R28.76 vs MP (250mg) R45.54.

The administration of corticosteroids as a continuous infusion would eliminate differences in consumable and labour costs. The relative efficacy of intravenous continuous and bolus dose corticosteroid therapy is not known.

8.7 CONCLUSIONS:

In conclusion, this study has shown an increased duration of hospital stay in patients with acute severe asthma treated with intravenous MP compared to those treated with HC. These differences, although small, are both statistically significant and consistent, but may for practical reasons have little bearing on the clinical choice of corticosteroid. There are indications that more severe asthmatics (as evidenced by their need for oral maintenance steroids) do better on HC. In general the decision to use HC or MP may be based on financial and labour-effectiveness considerations.

The simple and inexpensive study design used here has answered a relevant clinical question. This form of interventional survey can be used or adapted further for the evaluation of drug therapy and other management options, particularly in a setting such as the Asthma Unit. This could be a powerful clinical tool if used carefully and selectively. It could be particularly relevant in Africa where specific answers to local problems under local conditions are required and where classic experimental studies would place unrealistic demands on finances and personnel.

8.8 RECOMMENDATIONS:

In general, there is little difference between the efficacy of HC and MP in acute severe asthma. In the most severe acute attacks (eg in intensive care) the small advantage of HC may be more relevant. The fact that a difference between two high-dose steroid regimens could be shown in the present study raises serious questions regarding the current tendency to introduce lower dose and oral steroid regimens. The effectiveness of these regimens should be demonstrated under local conditions prior to their implementation.

CHAPTER 9: REFERENCES

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APPENDIX 1

ASTHMA UNIT OPERATING PROTOCOL
NOTES FOR MEDICAL OFFICERS IN THE EMERGENCY UNIT

A. INTRODUCTION:

Acute severe asthma is a potentially fatal condition. It has been shown that a frequent cause of death is under-treatment, due to inadequate assessment by the attending doctor. Often the doctor and patient both fail to appreciate the severity of the attack; objective tests such as the Peak Flow Rate, pulsus paradoxus and blood gases are therefore mandatory in the proper management of severe asthma attacks.

The "Asthma Room" is unique in this hospital in several respects:

(a) it is the only ward to which patients are admitted with a life-threatening illnesss without undergoing full clerking by a registrar and an intern;
(b) it has a very high turnover;
(c) many patients are re-admitted several times a year and staff get to know them;
(d) patients sit fully clothed in chairs.

These four factors all tend to militate against proper assessment and care of these severely ill patients. We therefore have a strictly disciplined monitoring procedure and our treatment schedules have been standardized to avoid confusion. If you ignore our procedures and schedules, you cannot expect the safety net to work - and I shall have difficulty in defending you in court.

Despite its obvious deficiencies, the Asthma Unit provides an essential sevice in Groote Schuur Hospital, by relieving the pressure on Medical Ward beds and making maximum use of

dedicated nursing staff. Some of the nurses in the Asthma Unit have been looking after asthmatics for years and they have a clear understanding of the value and limits of our monitoring procedures, our drug schedules and our criteria for referral and discharge. You ignore their suggestions at the patients' peril. New doctors often find their first day in the Asthma Unit a "harrowing" experience; but as they come to grips with our schedules and procedures, they invariably realise that these are not designed to create work but to reduce it, yet ensuring the maximum safety of the patient.
It is therefore imperative that you study these guidelines carefully. (You might as well learn how the system works by this easy way rather than through trial and error...)

B. DUTIES OF MEDICAL OFFICERS WITH RESPECT TO ASTHMA ROOM:

(a) Ante-Room Staff.

(i) New admissions are primarily seen by the ante-room staff unless the Asthma Unit medical officer is free. Severely ill asthmatics should be kept under observation in the Ante-room whilst blood gases and electrolytes are being done and the decision to refer to the Respiratory Intensive Care Unit is in the balance.

Patients who complain of chest pain should have a chest x-ray (to exclude pneumothorax or pneumonia) and an ECG if appropriate. Where a cough produces mucopurulent sputum a specimen should always be sent for microscopy, culture and sensitvity, Ziehl-Nielsson stain and fungal culture. Blood glucose should be checked where appropriate. If there is any question of theophylline toxicity being present, a blood specimen must be taken without delay.

(ii) Ante-room staff should retrieve the "Baseline Data Sheet" (if one exists) and complete an "Urgent Admission Data" form. Please tick the relevant boxes and do not use unconventional symbols. A new "Urgent Admission Data" form should be completed on every new admission.

(iii) The admitting medical officer should write up the treatment charts, including fluid balance chart and oxygen therapy.

(iv) The patient remains the responsibility of the clerking medical officer until he or she has done a formal hand-over to another medical officer (usually the Asthma Unit medical officer) in the presence of the patient.

(v) The Asthma Unit is designed for the care of straightforward severe asthmatics. Complicated cases, eg. with cardiac failure, metabolic disturbances, pneumonia or confusional states should not be admitted to the Asthma Unit. Equally end-stage Chronic Obstructive Lung Disease patients should not be admitted to the Asthma Unit, since they usually require a long hospital stay and deplete the Asthma Unit's resources.

(b) Asthma Unit Medical Officer

(i) Early morning ward round.

Read through the patients' records and complete "Baseline Data" forms for all patients that do not already have these. Note that patients need to be examined on a couch or bed, ideally. Note also that we use the American Thoracic Society criteria for the classification of dyspnoea. Update existing "Baseline Data" sheets.

Assess each patient from the point of view of response to therapy and complications of therapy. Perform appropriate blood tests. Personally check inhaler technique in all patients. Identify patients who do not know how to use their inhalers, new asthmatics and patients who seem to lack an understanding of their condition - for instruction by yourself later on, with the assistance of available nursing staff.

Arrange for Chest x-rays on patients who have not had one for more than one year, all new patients, patients who fail to show a response to 24 hours of therapy, patients with chest pain, patients with haemoptysis or pyrexia.

Decide which cases you would like to discuss on Dr. Louw's round. Get their Baseline sheets and chest x-rays ready.

(ii) Late morning round.
Write up discharge medicines and discharge letters. Ask nursing staff to make appointments for follow-up. See unstable cases. Discuss difficult cases with Dr. Louw. See results of investigations.

(iii) Afternoon round.
Get results of the electrolytes and theophylline levels requested that morning and make appropriate alterations to therapy. See all cases again. Check peak flow technique in cases that seem resistant to therapy. Check medication charts. Educate patients about their condition and use of inhalers. Discuss unstable or deteriorating cases with hand-over medical officer in ante-room in the presence of the relevant patients.

(iv) Investigations:
All patients should have a 6/60 and chest x-ray on the second morning of their stay in the Asthma Unit, i.e.

24-40 hours after admission, (unless they are due for discharge on that day). Theophylline levels should be done daily.

C. THERAPY:

(a) All patients receive Berotec by nebuliser, 1:4 ml saline, 4 hourly; in more distressed patients this can be given 2-hourly.

(b) Distressed asthmatics should be given oxygen by face mask (40%) when they are not using the nebuliser.

(c) Aminophylline: This drug should be used with extreme caution in patients:

(i) who have been using theophylline containing preparations prior to presentation;

(ii) with impairment of liver function;

(iii) with heart failure, since toxicity frequently develops. The administration regimen is described at the end of these notes.

(d) Intravenous salbutamol should be used in the following cases:

(i) Where aminophylline is contra-indicated;

(ii)Patients who appear not to have responded to aminophylline infusion after 6 hours (this might be due to the fact that therapeutic aminophylline levels have not been achieved, but no scientific basis for increasing the dose without knowing the theophylline level exists), or the patient appears to be resistant to aminophylline.

NOTE: That hypokalaemia often occurs in patients on high dose salbutamol. The electrolytes should be checked daily and supplemental potassium given as necessary.

(e) Methylprednisolone should be used in the following cases:

(i) All patients who required prednisone (or other corticosteroid) treatment in the preceding three months as part of their maintenance therapy.

(ii) All patients who have been in the Asthma Unit during the preceding four weeks.

(iii) All patients who fail to show a satisfactory response to the treatment outlined above within the

first ONE hour after admission. "Satisfactory response" may be defined as improvement with regard to general state of distress, reduction of tachycardia and pulsus paradoxus and improvement of PEFR by 50% or more. (e.g. PEFR on admisson = 60 going up to 90, or 90 on admission going up to 135 would constitute a satisfactory response in the first hour).

(iv) Patients who, on previous admissions to the Asthma Unit, showed a slow recovery curve and/or required IV methylprednisolone.

(f) Ipratropium Hydrobromide may be administered by nebuliser in cases that are particularly resistant to therapy or those who have significant adrenergic side effects.

(g) Antibiotics should be used in patients who produce yellow sputum. Always send a specimen to Bacteriology for microscopy, culture, sensitivity and fungal culture.

(h) Occasionally, dehydration may be responsible for a patients failure to improve. Features such as a dry tongue and reduced skin turgor should be noted.

(i) Pregnant asthmatics:

Available data indicate that the hypoxaemia caused by acute asthma leads to foetal wastage. All pregnant asthmatics in the Asthma Unit should receive continuous oxygen by nasal cannula. Treatment of these patients with steroids and bronchodilators should be along standard lines; there is no contra-indication to any of the drugs in acute asthma.

Upon discharge, all pregnant asthmatics should be given a follow-up appointment at the Allergy Clinic within one month.

(j) Bronchiectasis:

Patients with bronchiectasis who come to hospital with flare-ups should be admitted to a ward, since the mainstay of their therapy is antibiotics, postural drainage and education. These patients should not be admitted to the Asthma Unit.

(k) Allergic Bronchopulmonary Aspergillosis: (ABPA)
This condition is present in a significant proportion of severe asthmatics. It is due to a hypersensitivity reaction to the fungi that colonize the airways. Remember that a patch of pneumonia and upper lobe fibrosis may be due to this condition. Look for fungi in the sputum and send blood to bacteriology for aspergillus precipitins in suspected cases. Such cases should be seen in the Allergy Clinic for follow-up.

(l) Patients with chronic obstructive lung disease should only be admitted to the Asthma Unit if the Asthma Unit is relatively empty. Remember that inappropriate admissions put a strain on the nursing staff and reduce the amount of attention they can give the true asthmatics. COAD patients should be treated with bronchodilators and steroids and discharged when their effort tolerance has returned to their usual effort tolerance. COAD cases that come to the hospital frequently should be referred to the Respiratory Clinic for follow-up.
If the Asthma Unit is more than 50% full, no further COAD cases should be admitted - these patients should be admitted to the wards. The successful running of the Asthma Unit depends very much on Ante-room staff observing this rule.

D. MONITORING OF RESPONSE:

The doctor's failure to recogninse the severity of an attack is known to be a major cause of fatality in acute severe asthma. The premonition of death in a patient is often a significant prognostic symptom. A patient with explosive onset of bronchospasm calls for early, aggresssive intervention and extremely close monitoring.

In monitoring patients look at:-
(a) peak expiratory flow rate (PEFR) - severe if <90;

(b) width of pulsus paradoxus - severe if >20;
(c) pulse rate (less useful when drugs are being given) - severe if >130;
(d) pulse volume - a thready pulse is ominous - and signs of poor peripheral perfusion;
(e) general state of patient;
    (i) ability to breath-hold or speak;
    (ii) degree of distress as evidenced by the use of accessory muscles;
    (iii) evidence of confusion or
    (iv) exhaustion;
(f) cyanosis;
(g) character of respiration and onset of a "quiet chest".

Arterial blood gases should be done repeatedly in all cases that are:
(a) still judged to be severe after 1/2 hour of bronchodilator therapy;
(b) showing any evidence of deterioration;
(c) showing evidence of onset of exhaustion;
(d) thought to be cyanosed at any stage.

E. REFERRAL TO RESPIRATORY ICU AND EMERGENCY INTUBATION;

(a) Refer the following categories of patient for admission to the Respiratory ICU:
    (i) Patients that become progressively more exhausted;
    (ii) Patients that fail to respond to therapy and show a progressive rise in their P_aCO_2;
    (iii) Onset of metabolic acidosis and/or circulatory shutdown;
    (iv) Confused and uncooperative patients judged to be in severe status asthmaticus should be referred urgently.
(b) If there is delay before the Respiratory registrar can see the patient and if it appears that the patient is deteriorating further despite IV therapy, nebulizer

therapy and 40% oxygen by face mask, then an awake intubation should be performed after spraying the larynx with local anaesthetic.

F. REFERRAL TO MEDICAL WARD

(a) Patients with acute severe asthma with marked metabolic disturbances, such as diabetes or renal failure.
(b) Patients who fail to show a satisfactory improvement after 48 hours in the Asthma Unit, should be considered for admission; after 4 days the patient should definitely be admitted.
(c) Patients fulfilling the criteria under "E" above, when the respiratory intensive care is full.

G. ASTHMA DEATHS: RISK FACTORS

The following are features that have been recognised in association with asthma deaths.

(a) Incomplete asssessment of the severity of asthma and insufficient treatment;
(b) Morning dipping - death usually occurs in the early hours of the morning;
(c) Prolonged severe attacks of asthma;
(d) Frequent attacks of acute severe asthma;
(e) Large diurnal variations, i.e. pronounced early morning dipping;
(f) Progressive deterioration over months;
(g) Inadeqate use of corticosteroids to prevent attacks.

Factors c,d,e and f are generally problems that cannot be solved within two or three days in the Asthma Unit - such patients should therefore be admitted to a medical ward for stabilisation.

H. DISCHARGING PATIENTS:

1. INTRODUCTION:

Ideally an asthmatic should be kept under observation following the resolution of an acute severe attack until he/she has achieved a plateau corresponding to his/her best achievable PEFR and until "morning dipping" has been controlled. In our unit the pressure of numbers does not permit us to practice ideal medicine, so we have to make a compromise. In the running of the Asthma Unit there should always be an awareness of the balance between the number of chairs available for future admissions and the severity of the incumbents. When the Asthma Unit is relatively empty, one can afford to keep the more severe cases in for longer than is usually our practice.

2. ELIGIBILITY FOR DISCHARGE:

Patients may be deemed eligible for discharge if they satisfy all the following criteria:-

(i) No features of respiratory distress and able to walk to the toilet.

(ii) PEFR shows an upward trend or has plateaued at more than 70% of patient's best PEFR in the past year (or, if not available, predicted normal PEFR) and morning dipping is not below 50% of the patient's best PEFR in the past year (or predicted normal PEFR).

(iii) Patient feels that he/she would be able to cope at home.

3. THE DISCHARGE PRESCRIPTION:

Factors to be considered:

Although the format of this prescription would be similar for many of our patients, it should never be regarded as "standard". When you are writing the prescription and planning follow-up, the following questions should be considered:-

(a) How poor has the control, in general, of this patient's asthma been over the past year? Consider: Number of

times the patient required Asthma Unit therapy or IVI therapy elsewhere; number of days work missed; nocturnal waking; general effort tolerance.

Poor control might have been due to:-

(i) the patient's ignorance and consequent non-compliance (remedy: educate patient and arrange closer follow-up by the Day Hospital);

(ii) chronically under-treated asthma (remedy; look at the patient's maintenance therapy and decide at which step in the cascade [see below] he/she should really be maitained; write a clear letter to the Day Hospital in which you clearly state your recommendations);

(iii) the tailing-down-steroids-rebound syndrome: we have a substantial population of asthmatics with this syndrome, who regularly develop acute severe asthma whenever their prednisone falls below a certain threshold; they are often patients who require admission every 3 - 6 weeks (remedy: do not tail down their prednisone dose too rapidly and do not go below the critical threshold, often about 10-15 mg/day;

(iv) truly labile and truly resistant cases: when the abovementioned factors leading to poor control of asthma have been excluded, a few patients will be found to fall into this group (remedy: refer to Respiratory clinic for follow-up).

(b) Are there clearly definable factors that precipitate the attacks? Consider: atopic status, drugs that cause asthma, pets, hobbies, occupation and reactions to food and food additives. Clearly, advice regarding the avoidance of precipitating factors, where appropriate, is more valuable than thousands of rands of drugs.

(c) What is the nature of the present attack? If the present attack was of explosive onset and life-threatening severity, a very diligent search for the precipitating cause should be made. If none is found consideration should be given to supply the patient with a home nebuliser or with adrenaline for subcutaneous injection.

DRUGS TO BE USED:

(a) Principal drugs.

Almost all the patients will require all of the following drugs:

(i) Inhaled beclomathasone.

There has been an increasing awareness of the role that inflammation of the airways plays in patients with chronic, unstable asthma. Patients should be encouraged to use Beclomethasone inhalers regularly, even when they are feeling well. The usual dose is 2 puffs four times daily. In patients with a poor inhaler technique, Becotide rotahaler with rotacaps may be prescribed.

(ii) A B_2 adrenoreceptor stimulant inhaler: Ventolin, Berotec, Ipradol. Note that Ventolin is less expensive to the hospital than other preparations and probably has similar efficacy. Unstable patients should take 2 puffs 3 to 4 times a day regularly, but can take up to 16 puffs a day if necessary. Ensure that the patients' technique in using the inhaler is satisfactory. If incoordination cannot be remedied, prescribe Ventolin rotacaps.

(iii) Xanthines: Slow-release theophylline preparations: Nuelin SA, Euphyllin Retard or Theodur. Note that Nuelin SA is least expensive. If the dosage of these preparations is correctly adjusted, the need for Solphyllin falls away.

(iv) Prednisone/prednisolone: The majority of our patients are steroid dependent asthmatics who require a short booster course of prednisone before it is tailed down to their maintenance dose. The duration of the booster dose should be roughly equal to the present attack of asthma (e.g. 4 days of wheezing before admission and three days in the Asthma Unit = 7 days; therefore

prescribe prednisone 30 mg daily for 7 days before decreasing the dose). The rate of reduction in the dose should be tailored according to the lability of the patient's asthma and should also be slower in young asthmatics. It is safer to err on the side of a more prolonged course of steroids. Patients who are, in general, well controlled may require the following sort of regimen:

Prednisone 30 mg daily for 3 days
then 20 mg daily for 3 days
then 15 mg daily for 3 days
then 10 mg daily for 3 days
then 5 mg daily for 3 days

It is important to inform patients that, should their asthma deteriorate whilst they are tailing off their prednisone they should go back to the previous level of treatment and see a doctor the next day if their symptoms persist.

Patients who are, in general poorly controlled, may need to remain at each level in the regimen for a week or longer. Very poorly controlled asthmatics should be discharged on prednisone30 mg daily for two weeks, then 25 mg daily for two weeks and should have a follow-up appointment within three weeks of discharge.

(b) Additional options.

(i) Long-acting Salbutamol:

If the patient's symptoms appear to be satisfactorily controlled in general, but nocturnal cough and wheezing is a persistent problem, then adding Volmax 8mg nocte is often adequate to control this symptom.

4. SOCIAL AND EMOTIONAL FACTORS:

In some patients the stress produced by social or domestic pressures is such that it acts as a powerful precipitating factor of acute attacks. It is important to identify these cases and to intervene with the help of a social worker. Anxiety-induced acute severe asthma is no less severe than attacks precipitated by other factors and is recognised to carry a high mortality rate - probably because doctors are blinded by their concepts of pathogenesis.

5. THE DISCHARGE LETTER:

Every patient that is discharged from the Asthma unit should be given a letter to the doctor who normally looks after that patient. The patient should be clearly instructed to see his/her doctor within three weeks (or sooner, where appropriate). The letter should contain information regarding your assessment of the general control of symptoms and your recommendation regarding future long-term maintenance steroid preparations. For convenience, two standard discharge letter formats are available in the Asthma Unit. The first, headed "Recent Attack of Acute Severe Asthma" merely informs the patient's usual doctor of his/her admission and discharge prescription. The second, headed "Frequent Attacks of Acute Severe Asthma" informs the doctor of the recent attack, discharge prescription and draws attention to the fact that the patient's condition is generally unstable. Please ensure that the correct discharge letter format is used in each case.

6. FOLLOW-UP:

The following patients should be given appointments in the Allergy Clinic:

a. Patients with 3 or more acute severe attacks in the past 12 months.
b. Pregnant asthmatics.
c. Suspected cases of ABPA.
d. Suspected occupational asthma.

The following patients should be given follow-up appointments in the Respiratory Clinic:

a. Patients with suspected interstitial lung disease.
b. Asthmatics with a component of COAD, pulmonary fibrosis or cardiac failure.

Thus the Allergy Clinic is best geared to see pure asthmatics, whereas the Repiratory Clinic is best geared to see asthma accompanied by other lung disorders.

Other patients should be given a discharge letter with clear instructions to take their medications regularly and to go to their Day Hospital or general practitioner before they run out of medications.

I. DRUG ADMINISTRATION REGIMENS

1. INTRAVENOUS AMINOPHYLLINE:

A.LOADING DOSE REGIMEN:

Give 6mg/kg (ideal body mass) over 45 min. to patients who have not taken any theophylline containing preparations during the past 24 hours. If a history of some theophylline ingestion at home is obtained, but this is judged to have been inadequate to obtain therapeutic blood levels, then half the above loading dose may be given. If in doubt, go straight to the maintenance dose described below.

B. MAINTENANCE DOSAGE:

To be given as a 6-hourly infusion according to the patient's lean body mass and adjusted after 12 hours. Since the rate of excretion is slower in patients who do not smoke, are elderly, have liver or cardiac failure, different infusion rates apply to each category of patient

1. Young adult smokers (<60 years old): Maintenance 1.18 mg/kg/hr for 12 hours (i.e. 2 doses) then 0.94 mg/kg/hr.

2. Young adult non-smokers (<60 years old): Maintenance 0.82 mg/kg/hr for 12 hours then 0.59 mg/kg/hr.
3. Elderly patients (>60 years) or patients with cor pulmonale : Maintenance 0.71 mg/kg/hr for 12 hours then 0.35 mg/kg/hr. Note that in patients with Cor pulmonale care should be taken not to overhydrate patients.
4. Patients with cardiac failure/liver disease: Maintenance 0.59 mg/kg/hr for 12 hours then 0.18mg/kg/hr. Note that in patients with heart failure care should be taken not to overhydrate the patient and a double strength infusion over 12 hours might be preferable.

2. INTRAVENOUS SALBUTAMOL:

Put 10 mg salbutamol in 1 litre saline .

Loading dose: 0.285 micrograms/kg/min over 15 minutes.
Maintenance dose: 5 micrograms/minute.

The principal side-effect or toxic effect of salbutamol is sinus tachycardia Beta adenoreceptor agents cause hypokalaemia which may be severe; thus patients on a salbutamol infusion should have their electrolytes checked daily.

3. INTRAVENOUS CORTICOSTEROIDS:

All patients are given Methylprednisolone 125mg intravenously every 12 hours.

Dr S J LOUW
Respiratory Clinic
1990

APPENDIX 2

The data shown here reflects comparisons after excluding only the following categories:

1. Patients with known chronic obstructive lung disease, non-asthmatics and patients who received oral theophylline (n=38)
2. Patients not given intravenous steroids (n=47)
3. Patients transferred to the medical wards (n=19).

Therefore the patients shown here are compared irrespective of their need for additional therapy (salbutamol infusion) and without the application of criteria for the severity or reversibility of airflow limitation. Table 1 reflects the baseline demographic data and the comparison of outcomes is shown in Table 2. The only statistically significant comparison is that of HC vs MP in those who remained in the Asthma Unit after 48 hours. The consistent pattern showing a small superiority of HC over MP continues to be seen in the comparison of the duration of hospital stay and the time taken to achieve maximum PEFR.

APPENDIX TABLE 1: BASELINE DATA (PRIOR TO EXCLUSIONS)

	HYDROCORTISONE	METHYLPREDNISOLONE	P VALUE
	n=139	n=143	
Mean Age-years (±SD)	42.3±16.1	43.0±16.3	0.71 t test
Male Gender (%)	21.6	30.1	0.10 Chi-Square
Prior Maintenance Steroid* (%)	48.2	50.4	0.72 Chi-Square
Median Predicted PEFR (l/min)	411 [378/465]	409 [375/518]	0.50 Mann-Whitney U

* Data missing in 2 cases

[ ] Denotes values of 25th and 75th centiles

APPENDIX TABLE 2: COMPARISON OF OUTCOME (PRIOR TO EXCLUSIONS)

	HYDROCORTISONE n=139	METHYLPREDNISOLONE n=143	P VALUE
Mean Maximum PEFR			
-% of predicted (±SD)	77.6±21.4	80.9±20.6	0.21 t test
Median Hospital Stay-Hours	30 [18/42]	36 [18/48]	0.07 Median test
Median Hours to Maximum PEFR	20 [12/31]	22 [13/32.3]	0.31 Median test
Median PEFR at 24 Hours			
-% of predicted	66.8 [55/84] n=84	67.7 [54/87] n=93	0.85 Mann-Whitney U test
Median PEFR at 48 Hours			
-% of predicted	73.5 [57/82] n=27	57.6 [51/76] n=33	0.03 Mann-Whitney U test

[] Denotes values of 25th and 75th centiles